REMARKS

Reconsideration of this application is respectfully requested.

Claims 1-28 and 33-40 are pending in this application. Claims 1-27 and 34-39 have been withdrawn from consideration as being drawn to a nonelected invention. Thus, Claims 28, 33, and 40 are presented for reconsideration. Claim 28 has been amended to reinsert a semicolon that was unintentionally deleted in the previous amendment.

Claim 40 was objected to because of a typographical error in the phrase "pair of printers is labeled with fluorophores" in line 2. Correction was required. Claim 40 has been amended to recite that "primers" are labeled with fluorophores. Thus, the objection may be withdrawn.

Claims 28, 33, and 40 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Stanton in view of Larsen and further in view of Gelfand. This ground for rejection is respectfully traversed and reconsideration is requested for the following reasons.

In considering the non-obviousness of Applicant's invention, Applicant submits that the differences between genomic and post-genomic mechanisms must be considered to avoid confusion between genetic polymorphisms and physiological post-genomic controls of specific mRNAs for which several sets of mechanisms have been identified. Indeed, RNA editing is part of a singular subset of controls of expression of given proteins by living cells. The products expressed as mRNA of a given gene are continuously changed, adapted, or altered.

The problem solved by the present invention is not the detection of a polymorphism in a given subject, but rather the need for a method to analyze the diversity of products of one unique gene under different physiological or pathological conditions in the subject. This diversity, which depends on the activity and specificity of specialized enzymes, is difficult to identify and to quantify. Moreover, the complexity of this regulation for a single unique gene can generate several different isoforms of mRNA coding for functionally different isoforms of one protein. An understanding of the implicated regulation cannot be achieved without varying each of these transcripts during a given situation.

The pre-RNA editing of the 5-HT2cR gene is quite singular in this respect. This is due to the position of the 5 editing sites on 3 among 5 adjacent triplets of the coding sequence. The possible coding diversity (32 theoretical combined isoforms of mRNA) is thus localized on a total sequence of 15 nucleotides, which makes identification and quantification particularly difficult.

The first method to achieve this identification was based on cloning and sequencing. Unfortunately, this method, which remains a classic approach of identification, is not readily adapted to rapid quantification of the edited and non-edited mRNA isoforms. It requires the analysis of a great number (much more than 100) clones to achieve a relatively good statistical profile for quantification of all of the expressed 5-HT2cR mRNAs. (*See* Dracheva *et al.*, 2007 in Mol. Psychiatry).

Other authors (*see* Lanfranco MF et al., 2009 in J. of Neuroscience Methods) have recently published as innovative a real time PCR method, which makes it possible to discriminate only 4 of the 32 possible isoforms in tissues or cells. In their discussion,

these authors recognize the interest in the methodology now claimed by Applicant and published, for example, in Poyau *et al.*, 2007. But only Applicant has provided a credible solution by processing a sample of total RNA coming from tissue or cell extracts (Poyau *et al.*, 2007 and Chanrion *et al.*, 2008) to separate and quantify the total editing profile of 5-HT2cR mRNA.

This invention makes it possible to use capillary electrophoresis (CE) when SSCP is performed with certain primers leading to conformational differences of the expressed labeled strands. This had never been successfully achieved by others at the time this invention was made. The invention is useful for several applications, including drug discovery, diagnosis, and predictive medicine.

According to the Examiner, Stanton teaches a SSCP method for obtaining, under given analytical conditions, the editing profile of 5-HT2cR mRNA using a specific tissue sample or using a sample of a population of eukaryotic cells.

The Examiner cited Larsen as teaching high-throughput SSCP analysis by automated capillary electrophoresis and generating PCR amplified double-stranded DNA using fluorescently labeled primer, separation of single stranded DNAs by capillary electrophoresis, and obtaining the electrophoretic profile by reading the fluorescence and acquisition by means of a genetic analyzer detection system associated with fluorescence reader. Office Action at 7.

Neither of these documents, taken alone or in combination, suggests a CE-SSCP method associated with a fluorescent reader in order to separate and quantify the total editing profile of the 5-HT2cR mRNA using the pair of primers, SEQ ID NO:36 and SEQ ID NO: 37, as defined in Applicant's claims. In fact, the Examiner

acknowledged that Stanton and Larsen do not disclose primers of SEQ ID NOs: 36 and 37. Office Action at 8. Applicant points out that Gelfand does not disclose the primers of SEQ ID NOs:36 and 37. Thus, none of the cited references discloses these limitations in the claims.

It is the Examiner's burden to establish *prima facie* obviousness. *See In re Rijckaert*, 9 F.3d 1534, 1532, 28 U.S.P.Q.2d 1955 (Fed. Cir. 1933). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494 (C.C.P.A. 1970). Obviousness requires a suggestion of all the elements in a claim, *CFMT, Inc., v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342, 68 USPQ2d 1940 (Fed. Cir. 2003)). Here, the Examiner has not identified all the elements of Applicant's claims in Stanton, Larsen, or Gelfand. None of these references discloses or suggests SEQ ID NO:36 or SEQ ID NO:37. Thus, *prima facie* obviousness has not been established and the § 103 rejection is not sustainable for this reason alone.

The Examiner attempts to fill these gaps in the *prima facie* case of obviousness by contending that primers for PCR were known in the art as evidenced by Gelfand. The essence of the Examiner's argument is that Gelfand provides guidance for designing and selecting primers for any region of a target, and one having ordinary skill in the art would have been motivated to select any number of primers, including SEQ ID NOs. 36 and 37, for use in detecting the 5-HT2C receptor region of defined length during amplification or extension. Office Action at 8. Applicant disagrees.

A mere statement that the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish *prima facie* obviousness.

M.P.E.P. 2143.01 IV, citing *Ex parte Levengood*, 28 U.S.P.Q 1300 (Bd. Pat. App. Int. 1993). Here, the Examiner has not provided any findings of fact to support the contention that skilled artisans would design and synthesize SEQ ID NO:36 or SEQ ID NO:37. There is no evidence why or how the skilled artisan would choose these primers. Rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *In re Kahn*, 441 F.3d 977, 988, 78 U.S.P.Q.2d 1329, 1336. Thus, the Examiner is requested to provide reasons why the skilled artisan would have chosen SEQ ID NO:36 and SEQ ID NO:37 for use in the SSCP method.

Only with hindsight knowledge of Applicant's invention and its highly desirable advantages can one suggest that it would have been obvious to select and prepare primers of SEQ ID NOs: 36 and 37 based on Gelfand's teachings. The application of hindsight is inappropriate where the prior art does not suggest that these primers could reasonably be expected to manifest the properties and advantages that were found for them. *See KSR International Co. v. Teleflex Inc.*, 550 U.S.P.Q.2d 1385 (S. Ct. 2007) (recognizing "hindsight bias" and "ex post reasoning" as inappropriate in determining obviousness).

In conclusion, the focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person would have reasonably expected to have been able to do in view of that knowledge. This is so regardless of whether the source of that knowledge and ability was documentary prior art, general knowledge in the art,

or common sense. MPEP 2141 II. Here, the documentary prior art does not describe Applicant's primers. With regard to the general knowledge in the art, the Examiner has not provided any findings of fact that SEQ ID NO:36 and SEQ ID NO:37 were part of the general knowledge in the art. And surely one familiar with the complexities of mRNA transcription and processing would not contend that their selection and synthesis were a matter of "common sense." *See KSR Int'l v. Teleflex, Inc.*, 127 S. Ct 1727, 1741-42 (2007).

For these reasons, Applicant respectfully requests that the rejection under § 103(a) be reconsidered and withdrawn.

Please grant any additional extensions of time required to enter this response and charge any additional required fees to our Deposit Account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: June 19, 2009

By: Adam Brein Reg. No. 63,718
for Kenneth J. Meyers
Reg. No. 25,146
Phone: 202-408-4033
Fax: 202-408-4400
Email: ken.meyers@finnegan.com